SUMMARY STATEMENT

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Application Number: 1 R41 DK076502-01

MURPHY, TIMOTHY P MD
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Review Group: ZRG1 DIG-A (10)

Meeting Date: 03/10/2006
Council: MAY 2006
Requested Start: 07/01/2006

RFA/PA: PA06-007
PCC: NCD DDSB
Dual PCC: HHVOVN
Dual IC(s): HL

Project Title: Percutaneous mesenteric arterial flow modulation as treatment for morbid obesity

SRG Action: **
Human Subjects: 10-No human subjects involved
Animal Subjects: 44-Vertebrate animals involved - SRG concerns

Project Year	Direct Costs Requested
1	220,360
TOTAL	220,360

**NOTE TO APPLICANT: As part of the initial scientific merit review process, reviewers were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. At the study section meeting, those applications were discussed and assigned a priority score. All other applications, including this application, did not receive a score. Provided is a compilation of reviewers' comments prepared prior to the meeting, without significant modification or editing by NIH staff.

BUDGET MODIFICATIONS

1R41DK076502-01 MURPHY, TIMOTHY

CRITIQUE 1:

SIGNIFICANCE: The authors have identified morbid obesity as a clinically important problem for which optimal treatment has not yet been identified. As such, novel treatment methods are needed. The significance of the current proposal is the novel idea which the authors intend to study as a new and different approach to treatment of morbid obesity, that of the induction of visceral ischemia.

APPROACH: Chronic visceral ischemia is a serious condition in which blood flow to the small and large intestine is impaired; usually from atherosclerotic narrowing. Significant occlusion of two of the three visceral arteries (celiac, superior mesenteric, inferior mesenteric) is needed to induce chronic visceral ischemia. Although usually painful stimuli, such as cutting with a knife, or stabbing with a needle do not induce pain in the intestines, the two most powerful inducers of pain are distention and ischemia. In patients with chronic visceral arterial occlusion, blood flow to the intestines can't increase in response to a meal. Mucosal flow comprises 50% of flow to the intestines in the fasting state, and this increases to 75% after a meal. The progression from minor symptoms to transmural infarction is unpredictable and mortality of transmural infarction is 80%.

The inability to increase visceral blood flow and the resultant ischemia in response to a meal creates pain, which in turn causes affected individuals to avoid food, or eat only small amounts – "food fear". Consequently, affected individuals lose weight. It is this aspect that the authors intend to exploit in their admittedly novel approach to the treatment of morbid obesity. Turning conventional therapy on its head, instead of using stents to open narrowed vessels, this proposal seeks to place stents to decrease visceral blood flow, inducing "food fear". The concept of establishing a negative stimulus-response in the morbidly obese is not new, as the pouch restriction and distention in response to overfeeding, or the gas bloat and diarrhea seen after eating too many sweets associated with gastric bypass are similar examples.

There are four aims. The first proposes to create balloon-expandable stents for purposes of this proposal. There is no discussion of why currently existing stents might not work, at least for proof of principle. The authors present *in situ* data for a 30 kg swine that gives the size of the cranial mesenteric artery (analogous to human superior mesenteric artery) as 6 mm outer diameter. It is probably important to know whether in the fed state the proximal artery dilates as well as the downstream vascular bed. Most atherosclerotic lesions are fixed, unlike normal arteries. This could be evaluated *in vivo* with duplex ultrasonography.

Aim 2 is to study mesenteric arterial flow in the swine visceral circulation to understand collateral pathways of importance and devise ways to occlude these pathways. I note that the authors appear to believe that the 6 mm artery in the 30 kg swine is somewhat at the limits of their catheterization abilities, so how small collaterals are likely to be embolized is not clear. There is no plan for obtaining flow data that might suggest how much limitation is necessary to effect the desired weight loss. There are no specific experiments presented to show exactly how the authors intend to satisfy Aim 2.

Aim 3 is to use data supplied from the first two aims to perform a study in which adult swine are randomized to reducing stent or sham catheterization. The randomization is said to be after arteriography, the rationale for which is unclear. They will then observe the animals to see if one group gains more weight. There appear to be 5 swine in each group, however there is no discussion of how these sample sizes were generated. Although maintenance of swine for such a study is resource intensive, a biostatistician should help decide how many should be treated in each group for differences in weight loss. The authors are predicting a 20 pound difference in weight, but there is no rationale for this choice. The 20 pound difference is a delta of one pound per three days. There is no discussion of what signs they will be observing to determine if the swine are in distress (e.g. manifest food fear).

Aim 4 will use tolazoline, an alpha adrenergic blocker, to mimic increased flow associated with a meal. The plan is to first place the stent, then dilate the luminal diameter so the resting pressure across the stent is nil. Then, tolazoline, 25 mg, will be used to see if a pressure gradient can be detected. The authors do not discuss what they intend to do if no gradient can be seen after infusion of the tolazoline.

INNOVATION: This is an innovative idea, and looks at the treatment of morbid obesity in an entirely novel way.

INVESTIGATORS: Appear to have the expertise to carry out the required studies.

ENVIRONMENT: Adequate.

VERTEBRATE ANIMALS: Appears appropriate. As a part of the scientific design, however, more detail on exactly how the investigators will score pain and food aversion must be addressed.

OVERALL EVALUATION: The strength of this application is the novelty of the approach and the stent fabrication expertise of the investigators. Weaknesses include a basic conceptual issue about whether it is ethical to induce pain as an approach to trying to get patients to lose weight. Further, given the significant degree to which arterial occlusion is necessary in humans to get chronic visceral ischemia, it is unclear whether adequate occlusive stenting can be done safely. All issues of translation into the clinical setting aside, for the reasons mentioned above, it is unclear that the swine studies proposed will answer the question of whether or not this is a viable approach.

BUDGET: I question the charge of administrative (secretary/clerical). Otherwise the budget appears adequate.

CRITIQUE 2:

SIGNIFICANCE: Obesity is a significant health problem in the US and worldwide. Therefore, developing new therapeutic modalities for inducing weight loss is a very relevant area of investigation. However, in this application the PI is proposing to introduce a stent into the arterial blood vessels of the small intestine to induce a serious condition resembling chronic intestinal ischemia. This approach is likely unfeasible and unethical.

APPROACH: This is the first submission of an R41 STIR application to develop a new treatment modality for obesity based upon reducing blood flow to the small intestine. The approach this investigator is taking to address this important issue is seriously flawed since the PI is effectively suggesting the induction of a serious disease state, i.e., chronic abdominal angina and mesenteric ischemia to induce weight loss. Thus, the weight loss will derive from the pathological condition associated with severe symptoms in many cases, including diarrhea, malabsorption and significant abdominal pain. How would one control for the amount of ischemia generated in the small intestine to avoid, for example, intestinal infarction? Unfortunately the PI has not discussed any of these important issues related to the applicability of this methodology to the human condition within the experimental design of this application.

INNOVATION: This proposal is certainly innovative; however, it is unlikely to be applicable to obese patients without serious complications.

INVESTIGATORS: Dr. Murphy is a professor of research at Brown Medical School. He is an established investigator in the field of vascular biology, with expertise in vascular stenting. He is collaborating with Quechan Engineering, Inc. It is unclear from the proposal who in this company is collaborating in these studies. Dr. Murphy is certainly qualified to perform these studies.

ENVIRONMENT: Appropriate as described.

VERTEBRATE ANIMALS: The five points that are required for vertebrate animals are not appropriately described.

OVERALL EVALUATION: This is a new R41 STIR application to develop a novel therapeutic modality to treat obesity. The main problem with this grant proposal is that the PI is proposing to induce a serious disease state in obese patients to cause them to fear food, experience serious symptoms of intestinal ischemia and then lose weight. This proposal raises significant ethical concerns and there is highly unfeasible. Therefore, the proposal is not recommended for further consideration.

BUDGET: Appropriate as described.

CRITIQUE 3:

SIGNIFICANCE: Morbid obesity is a significant public health problem and is responsible for placing an enormous financial burden on our society. It is also a major risk factor for cardiovascular diseases and diabetes. The main therapy against obesity consists of various weight-loss programs based on stimulating exercise and restricting dietary intake. Other more radical treatments are surgically based and include gastric bypass. Such treatments are not free of complications (1-2 % mortality) and are generally reserved for the most severely obese patients. The investigators propose a radically new method based on well-known endovascular techniques used commonly to treat patients with vascular diseases. This approach, placing a stent-graft in the superior mesenteric artery to reduce blood flow and thus create a controlled form of mesenteric ischemia, is somewhat innovative and if successful could prove quite significant despite a number of major problems and ethical consideration.

APPROACH: The goal of the proposal is to induce a “controlled” form of mesenteric ischemia by placing a stent-graft in the superior mesenteric artery in order to limit food intake. The resultant “food fear” would force obese patients to eat small meals to avoid causing excruciating abdominal pain due to the newly created mesenteric ischemia. There are a number of major problems with this proposal:

Stent graft design: There are a number of commercially available stents and stent grafts, yet the investigators do not provide any explanation as to why they need to design a new type of stent, especially in view of the fact that such stent grafts have been used for the same purpose (i.e. reducing blood flow) in the case of Transjugular Portosystemic Shunts (TIPS) for patients with portal hypertension. The same dumbbell shape that the investigators want to test to induce mesenteric ischemia has already been used successfully with commercially available stent grafts to reduce porto-systemic venous flow. The rationale for a new stent design must be provided.

Experimental protocol: The need for randomization after the diagnostic angiogram is not explained and does not appear justified unless it is done to control for the effects of the surgery.

Unexplained potential problems: No remedy to potential problems encountered during the conduct of the proposed experiments is given. For example, what if the stent graft does not reduce blood flow enough? Or if on the contrary, the stent graft is too occlusive, which can happen in vessels of that size (6 mm)? The problem of distal flow is not addressed at all. Not only does it have practical implications from the standpoint of successfully completing the experiments, but it does also have major ethical considerations if the degree of flow reduction can not be totally controlled. It could lead to irreversible ischemia requiring some form of surgical intervention if at all.

Ethics: There should be serious reservations about conducting the proposed experiments in pigs given the fact that evaluating and quantifying the degree of mesenteric ischemia-related pain and “food fear” is not addressed at all by the investigators. It might not be feasible to do so, but at the very least the investigators should have studied that problem in detail. Translating this method to humans is even more problematic from the ethical standpoint. How can we justify inducing severe abdominal pain every

time someone eats? Furthermore, the problem of irreversibility i.e. in case the pain is intolerable for the patient, is not addressed at all.

INNOVATION: The concept of treating morbid obesity via endovascular means is highly innovative, although it is extremely controversial ethically. However, the use of stents or stent-grafts as in this case to limit flow in a vascular structure is not new as it has been used not uncommonly for patients suffering from portal hypertension treated with Transjugular Portosystemic Shunts (TIPS). Some of these patients can experience a high degree of encephalopathy as a result of increased flow from the portal vein to the hepatic veins. In such instances (published reports by Haskal), a stent-graft can be shaped as described in the current protocol in order to reduce blood flow without causing complete occlusion.

INVESTIGATORS: The PI is a well respected interventional radiologist with a vast experience in the field of peripheral vascular interventions. His team should be able to accomplish some of their goals, especially the creation of a stent graft, but it is not sure whether the remaining goals will be achieved.

ENVIRONMENT: Appropriate for the scope of the studies described in the proposal.

VERTEBRATE ANIMALS: Serious reservations about the experimental design of the study involving the animals, specifically Aims 2-4. No explanation is provided to justify the number of animals in terms of reaching statistical significance. The investigators did not address how they will evaluate mesenteric ischemic pain or quantify food fear in the pigs. Measuring weight loss is perhaps scientifically relevant but certainly not ethically correct. This must be dealt with in some fashion. The proposal has not yet been submitted to ACUC.

BIOHAZARDS: No issue.

OVERALL EVALUATION: Although this proposal deals with a critically important issue plaguing our health care system, namely obesity and more specifically morbid obesity, it is far from convincing from the scientific standpoint. The notion of using endovascular minimally invasive techniques to create a “controlled” form of mesenteric ischemia to reduce food intake through induction of food fear may be innovative but it is largely untested and the proposal is filled with unanswered questions that may prove to be insurmountable. The experimental design is also generally weak and potential problems are not dealt with appropriately.

BUDGET: Appropriate except the 50% salary support for an administrative secretary, as it does not appear clear at all what the need for this person will be throughout the work proposed in this application.

MEETING ROSTER

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CENTER FOR SCIENTIFIC REVIEW
ZRG1 DIG-A (10) B
March 10, 2006

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

NOTIFICATION OF SCIENTIFIC REVIEW ACTION

Release Date: 03/23/2006

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Our Reference: 1 R41 DK076502-01 ZRG1 DIG-A (10)

The scientific merit review of your application, referenced above, is complete. As part of this initial review, reviewers were asked to provide written evaluations of each application and to identify those with the highest scientific merit, generally the top half of applications they customarily review, for discussion at the meeting and assignment of a priority score. Your application did not receive a score. Unscored applications are neither routinely reviewed at a second level by a national advisory council or board nor considered for funding.

Enclosed is your summary statement containing the reviewers' comments. You should call the program official listed below to discuss your options and obtain advice.

Christine Densmore
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If you choose to resubmit, it is important to respond specifically to comments in the summary statement, as outlined in the instructions in the PHS 398 application kit (http://grants1.nih.gov/grants/funding/phs398/phs398.html).

Enclosure

cc: Business or institutional official of applicant organization

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